A B C D

Boehringer Ingelheim
Pharmaceuticals, Inc.

Roger Citron, Pharm D
Montana Medicaid
111 North Sanders Street
Helena, MT 59601

April 17, 2008

DRUG INFORMATION

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (800) 542-6257
Telefax (800) 821-7119
E-Mail: druginfo.rdg@boehringer-ingelheim.com

Dear Dr. Citron:

Thank you for discussing SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) and ATROVENT ® HFA Inhalation Aerosol (ipratropium bromide) with your Boehringer Ingelheim Pharmaceuticals, Regional Manager, State Government Affairs, Penny Atwood. You requested post 2006 clinical data for formulary review at the upcoming Pharmacy and Therapeutics Committee Meeting.

If you did not request this information, please contact our Drug Information Unit Call Center at 1-800-542-6257 (option #4).

Included in this packet are the following SPIRIVA-related documents:

- Bibliography (2007 – present)
- Package Insert (December 2007 version)
- Efficacy and Safety Letter
- Asthma Therapy Letter
- Combined with Inhaled Corticosteroids Letter
- Hyperinflation Letter
- Use in Patients Previously Naïve to Maintenance Therapy Letter
- Salmeterol Plus Fluticasone Combined with SPIRIVA Letter
- INSPIRE Trial Letter
- SPIRIVA and Possible Elevated Risk of Stroke Letter
- UPLIFT Trial Letter

The July 2007 version of Package Insert is included for ATROVENT.

For additional information and the most recent update (2007) to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guideline, please visit www.goldcopd.com. For currently ongoing trials with ATROVENT and SPIRIVA, please visit www.clinicaltrials.gov.

SPIRIVA HandiHaler is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Any other use not included in the package insert(s) is an investigational use and cannot be recommended by Boehringer Ingelheim Pharmaceuticals, Inc.

ATROVENT HFA Inhalation Aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. Any other use not included in the package insert(s) is an investigational use and cannot be recommended by Boehringer Ingelheim Pharmaceuticals, Inc.

Thank you for your interest in SPIRIVA HandiHaler and ATROVENT HFA Inhalation Aerosol. If you should have any further questions, please do not hesitate to contact the Drug Information Unit.

Sincerely,

Agnieszka Machate, Pharm D.

Manager, Medical Information
Drug Information Unit
druginfo@rdg.boehringer-ingelheim.com
AMACHATE/2008-007193

Bibliography: 2007 – present

Tashkin D.P. Littner M. Andrews C.P. Tomlinson L. Rinehart M. Denis-Mize K. Concomitant treatment with nebulized formoterol and tiotropium in subjects with COPD: A placebo-controlled trial. Respiratory Medicine 2008; 102(4): 479-487.

Teruhisa T. Seiji M. Yoshitomo O. Fumihiro T. Seiki H. Efficacy of tiotropium inhalation in COPD patients undergoing pulmonary lobectomy. Therapeutic Research 2008; 29(1): 69-72.

Criner G.J. Sharafkhaneh A. Player R. Conoscenti C.S. Johnson P. Keyser M.T. Cassino C. Efficacy of tiotropium inhalation powder in African-American patients with chronic obstructive pulmonary disease. COPD: Journal of Chronic Obstructive Pulmonary Disease 2008; 5(1): 35-41.

Moita J. Barbara C. Cardoso J. Costa R. Sousa M. Ruiz J. Santos M.L. Tiotropium improves FEV_1 in patients with COPD irrespective of smoking status. Pulmonary Pharmacology and Therapeutics 2008; 21(1): 146-151.

Bateman E.D. van Dyk M. Sagriotis A. Comparable spirometric efficacy of tiotropium compared with salmeterol plus fluticasone in patients with COPD: A pilot study. Pulmonary Pharmacology and Therapeutics 2008; 21(1): 20-25.

Wedzicha J.A. Calverley P.M.A. Seemungal T.A. Hagan G. Ansari Z. Stockley R.A. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. American Journal of Respiratory and Critical Care Medicine 2008; 177(1): 19-26.

Magnussen H. Bugnas B. van Noord J. Schmidt P. Gerken F. Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. Respiratory Medicine 2008; 102(1): 50-56.

Chan C.K.N. Maltais F. Sigouin C. Haddon J.M. Ford G.T. A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. Canadian Respiratory Journal 2007; 14(8): 465-472.

Bos I.S.T. Gosens R. Zuidhof A.B. Schaafsma D. Halayko A.J. Meurs H. Zaagsma J. Inhibition of allergen-induced airway remodelling by tiotropium and budesonide: A comparison. European Respiratory Journal 2007; 30(4): 653-661.

Powrie D.J. Wilkinson T.M.A. Donaldson G.C. Jones P. Scrine K. Viel K. Kesten S. Wedzicha J.A. Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD. European Respiratory Journal 2007; 30(3): 472-478.

Verbanck S. Schuermans D. Vincken W. Small airways ventilation heterogeneity and hyperinflation in COPD: Response to tiotropium bromide. International Journal of COPD 2007; 2(4): 625-634.

Gonlugur U. The effect of tiotropium on the pulmonary diffusing capacity. Methods and Findings in Experimental and Clinical Pharmacology 2007; 29(8): 535-537.

Kerstjens H.A.M. Bantje T.A. Luursema P.B. Sinninghe Damste H.E.J. De Jong J.W. Lee A. Wijker S.P.C. Cornelissen P.J.G. Effects of short-acting bronchodilators added to maintenance tiotropium therapy. Chest 2007; 132(5): 1493-1499.

Matsuyama W. Mitsuyama H. Koreeda Y. Higashimoto I. Osame M. Arimura K. Use of tiotropium bromide for pre-operative treatment in chronic obstructive pulmonary disease patients: Comparison with oxitropium bromide. Internal Medicine 2007; 46(17): 1373-1380.

Buhling F. Lieder N. Kuhlmann U.C. Waldburg N. Welte T. Tiotropium suppresses acetylcholine-induced release of chemotactic mediators in vitro. Respiratory Medicine 2007; 101(11): 2386-2394.

Hodder R. Kesten S. Menjoge S. Viel K. Outcomes in COPD patients receiving tiotropium or salmeterol plus treatment with inhaled corticosteroids. International Journal of COPD 2007; 2(2): 157-167.

Rice K.L. Kunisaki K.M. Niewoehner D.E. Role of tiotropium in the treatment of COPD. International Journal of COPD 2008; 2(2): 95-105.

Travers J. Laveneziana P. Webb K.A. Kesten S. O'Donnell D.E. Effect of tiotropium bromide on the cardiovascular response to exercise in COPD. Respiratory Medicine 2007; 101(9): 2017-2024.

Cazzola M. Ando F. Santus P. Ruggeri P. Di Marco F. Sanduzzi A. D'Amato M. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulmonary Pharmacology and Therapeutics 2007; 20(5): 556-561.

Rodrigo G.J. Nannini L.J. Tiotropium for the treatment of stable chronic obstructive pulmonary disease: A systematic review with meta-analysis. Pulmonary Pharmacology and Therapeutics 2007; 20(5): 495-502.

Asamoto H. Iwasaki A. Clinical effects of tiotropium bromide (Spiriva) in the stable COPD. Therapeutic Research 2007; 28(6): 1183-1189.

Santus P. Centanni S. Morelli N. Di Marco F. Verga M. Cazzola M. Tiotropium is less likely to induce oxygen desaturation in stable COPD patients compared to long-acting beta$_2$-agonists. Respiratory Medicine 2007; 101(8): 1798-1803.

Breekveldt-Postma N.S. Koerselman J. Erkens J.A. Lammers J.-W.J. Herings R.M.C. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. Respiratory Medicine 2007; 101(7): 1398-1405.

Pieper M.P. Chaudhary N.I. Park J.E. Acetylcholine-induced proliferation of fibroblasts and myofibroblasts in vitro is inhibited by tiotropium bromide. Life Sciences 2007; 80(24-25): 2270-2273.

De Luise C. Lanes S.F. Jacobsen J. Pedersen L. Sorensen H.T. Cardiovascular and respiratory hospitalizations and mortality among users of tiotropium in Denmark. European Journal of Epidemiology 2007; 22(4): 267-272.

Fardon T. Haggart K. Lee D.K.C. Lipworth B.J. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. Respiratory Medicine 2007; 101(6): 1218-1228.

Cazzola M. Gabriella Matera M. The additive effect of theophylline on a combination of formoterol and tiotropium in stable COPD: A pilot study. Respiratory Medicine 2007; 101(5): 957-962.

Gelb A.F. Taylor C.F. McClean P.A. Shinar C.M. Rodrigues M.T. Gutierrez C.A. Chapman K.R. Zamel N. Tiotropium and simplified detection of dynamic hyperinflation. Chest 2007; 131(3): 690-695.

Incorvaia C. Galeazzo Riario-Sforza G. Pravettoni C. Dugnani N. Paterniti F. Pessina L. Fumagalli M. Effects of replacing oxitropium with tiotropium on pulmonary function in patients with COPD: A randomized study. Respiratory Medicine 2007; 101(3): 476-480.

Verbanck S. Schuermans D. Vincken W. Small airways ventilation heterogeneity and hyperinflation in COPD: response to tiotropium bromide. International Journal of COPD 2007; 2(4): 625-34.

Eguchi Y. Tateishi Y. Umeda N. Yoshikawa T. Kamoi H. Kanazawa H. Kudoh S. Hirata K. Fujimoto S. Effects of tiotropium or combined therapy with salmeterol on hyperinflation in COPD. Osaka City Medical Journal 2007; 53(1): 25-34.

Efficacy and Safety

SPIRIVA is a long-acting, specific antimuscarinic agent, often referred to as an anticholinergic. In the airways, SPIRIVA exhibits pharmacological effects through prolonged inhibition of M_3 receptors, a subtype of muscarinic receptors, at the smooth muscle, leading to bronchodilation.

According to the latest Update to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines, regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators and is recommended as maintenance therapy. Long-acting inhaled bronchodilators now include two classes of medication, long-acting beta-adrenergic agonists and the newly available long-acting anticholinergic, SPIRIVA HandiHaler (tiotropium bromide inhalation powder), which is considered by GOLD to be a first-line maintenance medication for COPD. Anticholinergic inhalation therapy has a prominent place in many consensus statements (GOLD: NHLBI/WHO Workshop Report Executive Summary. Available at: www.goldcopd.com ; ATS : Celli BR, et al. *Euro Respir J* 2004;23(6):932-946).

Efficacy

The approval of SPIRIVA, by the Food and Drug Administration, was based on a review of data from four one-year and two six-month studies involving 2,663 patients with COPD (1,308 receiving SPIRIVA) (Casaburi R et al. Eur Respir J 2002;19:217-224, Vincken W et al. Eur Respir J 2002;19:209-216, Donohue JF et al. Chest 2002;122:47-55, Brusasco V et al. Thorax 2003;58:399-404). These studies demonstrated that SPIRIVA was safe and effective in the maintenance treatment of bronchospasm associated with COPD. The trials were all similar in design: (multi-center, randomized, double-blind). Two of the one-year studies were placebo-controlled and compared SPIRIVA 18 mcg once daily, (n=550) to placebo (n=371) in COPD patients in the United States. The other two one-year studies compared SPIRIVA 18 mcg once daily, (n=356) to ipratropium bromide, 42 mcg four times daily, (n=179) in COPD patients in the Netherlands and Belgium. The two six-month studies were multinational (18 countries) and compared SPIRIVA 18 mcg once daily, (n=402) to salmeterol, 50 mcg twice daily (n=405) and placebo (n=400). SPIRIVA was administered via the HandiHaler® and salmeterol via a metered dose inhaler. The active comparator studies used a double-dummy design.

All four one-year trials and the two six-month trials used a similar protocol. Since the two placebo-controlled one-year trials used an identical protocol, data from these two trials were pooled and analyzed as one combined trial. Similarly, the two ipratropium-controlled one-year trials were also pooled and analyzed as one combined trial and the two six-month trials comparing SPIRIVA with placebo and salmeterol were also pooled and analyzed as one combined trial. The only difference between the two six-month trials was that serial spirometry for one study focused on 12-hours (Trial A) while the other utilized 3-hour serial spirometry (Trial B).

Bronchodilator efficacy, of the 18 mcg SPIRIVA powder capsules orally inhaled once daily via the HandiHaler in patients with COPD, was the primary endpoint for all of the studies. Trough forced expiratory volume in one second (FEV_1) response was measured for all studies and was defined as the change from baseline in FEV_1 (trough FEV_1 was the mean of two FEV_1 readings at the end of the dosing interval). Dyspnea was a co-primary objective in the six-month studies and a secondary objective in the four one-year studies. Dyspnea was measured through the Baseline Dyspnea Index (BDI) and the Transition Dyspnea Index (TDI) focal score. The TDI focal score is a sum of three components (Functional Impairment, Magnitude of Task and Magnitude of Effort) and has a range from -9 to 9. Additional study outcomes included: average and peak FEV_1 response, forced vital capacity (FVC), morning and evening peak expiratory flow rate (PEFR) measurements, use of concomitant respiratory medications, number/length of COPD exacerbations, and the St George's Respiratory Questionnaire (SGRQ). The Medical Outcomes Study Short-Form 36 (SF-36) was also evaluated in the one-year trials.

Inclusion for all trials required patients to be 40 years of age or older with a smoking history of more than ten pack-years. For the one-year trials patients were required to have relatively stable airway obstruction with a $FEV_1 \leq 65\%$ of predicted normal and $FEV_1 \leq 70\%$ of FVC. For the six-month trials, as with the one year trials, patients were required to have relatively stable airway obstruction defined as $FEV_1 \leq 60\%$ of predicted and FEV_1 / FVC $\leq 70\%$.

Overall, for all six trials, the patient population was 65% to 85% males and more than 95% were Caucasian. The mean age was about 65 years (range of 39 to 87 years) and, patients were permitted to use albuterol metered dose inhaler as needed, stable doses of theophylline, inhaled glucocorticosteroids and the equivalent of 10 mg/day or less of oral prednisone. For all trials (individually) an adequate number of patients were enrolled to ensure a response with at least 80% power. Results from the pooled trials are detailed below. In addition, interim results from a scheduled 13-week timepoint analysis, were published for one placebo (Casaburi et al. Chest 2000;118:1294-1302) and one ipratropium study (Van Noord et al. Thorax 2000;55:289-294).

- *SPIRIVA vs Placebo*

Casaburi et al. reported that during the one-year placebo-controlled trials, 921 patients (550 receiving tiotropium and 371 receiving placebo) were randomized using a 3:2 allocation ratio for SPIRIVA and placebo; greater number of patients were allocated to the tiotropium group to achieve a greater safety exposure for SPIRIVA. For both trials, patients received drug treatment for 49 weeks, although they are referred to as one-year trials for convenience. A significantly greater percent of patients in the SPIRIVA group (81.3%) completed all visits compared to those in the placebo group (72.2%; $p<0.05$). Fewer patients failed to complete due lack of efficacy (2.4%) in the SPIRIVA group than in the placebo group (7.0%; $p<0.05$).

At the screening visit, the mean FEV_1 was 1.01 L (SPIRIVA) versus 0.99 L (placebo); 39.1% and 38.1% predicted normal FEV_1. No statistically significant differences were identified for baseline characteristics between the two groups. Spirometric testing was conducted at baseline and on treatment day 1 and after 1, 7, 13, 25, 37, and 49 weeks of therapy. FEV_1 and FVC were recorded one hour and just prior to dosing and at 30, 60, 120, 180 minutes post administration. Dyspnea was assessed at baseline with the BDI. Changes in dyspnea from baseline were measured using the TDI at Day 50, Day 92 and every three months thereafter.

SPIRIVA produced a statistically significant bronchodilator response, as measured by FEV_1, within 30 minutes following the first dose of SPIRIVA ($p < 0.01$). With daily SPIRIVA therapy, the mean pre-dose FEV_1 (trough values) were elevated by 0.11 L to 0.13 L (11% to 13%) over baseline; this was superior to placebo by 0.12 L to 0.15L at various assessment days ($p < 0.01$). The mean FEV_1 average response, during the first three hours following SPIRIVA, ranged from 0.19 L to 0.22 L (19% to 22%); this was superior to placebo by 0.14 L to 0.22 L. In addition, significant differences from placebo were observed for the peak response. SPIRIVA produced sustained bronchodilation throughout the study with no evidence of tachyphylaxis.

The FVC response mirrored the FEV_1 response. Mean increase in trough FVC ranged from 0.26 L to 0.29 L (12% - 13%) over baseline and ranged from 0.42 L–0.51 L (19% to 23%) over baseline for three hour post-treatment. The difference between tiotropium and placebo was highly statistically significant ($p<0.01$).

The TDI focal score revealed a significant improvement in breathlessness, which was achieved by the first assessment (day 50) and maintained for the entire year in the tiotropium group, compared to placebo at baseline. Differences ranged from 0.81 - 1.14 ($p < 0.001$ at all time points). Also, a significantly greater percentage of patients treated with SPIRIVA (42% to 47%) showed a clinically meaningful improvement (TDI focal score of one or more) than those treated with placebo (29% to 34%; $p < 0.01$).

SPIRIVA also demonstrated improvement in COPD exacerbations, as the proportion of patients experiencing at least one COPD exacerbation was lower in the SPIRIVA group (36%) vs. placebo (42%) (14% reduction; $p < 0.05$). Time to onset of first exacerbation was significantly delayed vs. placebo ($p = 0.011$). Hospitalizations associated with exacerbations were significantly less ($p = 0.019$) in the SPIRIVA group (0.086 per patient year) compared to placebo (0.161 per patient year) a 47% reduction. And, SPIRIVA patients spent fewer days hospitalized secondary to exacerbations (0.6 per patient year vs 1.2 per patient year; $p=0.023$). In addition, PEFRs (morning and evening) were greater for the SPIRIVA group compared to placebo ($p < 0.05$). Health-related quality of life as measured by SGRQ demonstrated that SPIRIVA was significantly more effective than placebo with improvements in each domain

as well as in total score and improvement in quality of life was confirmed with the SF-36 ($p < 0.05$). SPIRIVA patients also used significantly less albuterol than patients treated with placebo during the last trial week ($p < 0.01$).

- *SPIRIVA vs Ipratropium bromide*

Vincken et al. reported that the two one-year ipratropium-controlled trials randomized a total of 535 patients (356 receiving tiotropium and 179 receiving ipratropium) using a 2:1 allocation ratio (SPIRIVA and ipratropium. A greater percent of patients in the SPIRIVA group (84.8%) completed these trials compared to ipratropium (78.8%), and fewer patients failed to complete due to lack of efficacy (0.8% SPIRIVA vs. 1.7% ipratropium), however, these differences were not statistically significant ($p = 0.08$ and $p > 0.05$ respectively).

The patient population was made up of slightly milder COPD patients, compared to the placebo-controlled trials, based on their mean screening FEV_1 of 1.25 L (SPIRIVA) versus 1.18 L (ipratropium); 41.9% and 39.4% predicted normal FEV_1. Patient demographics were comparable across treatment groups. Spirometry was conducted at screening and on day 1 as well as after 1, 7, 13, 26, 39, and 52 weeks of therapy. Testing was performed one hour before drug administration, and at 30, 60, 120, and 180 minutes post dosing (and at 240, 300, and 360 minutes on day 1 and at 1, 7, and 13 weeks). Dyspnea was assessed at baseline with the BDI and changes in impairment were measured with the TDI at Day 8, Day 92 and every three months thereafter.

SPIRIVA produced a significant bronchodilator response within 30 minutes after the first dose and by the end of the first week, mean trough FEV_1, for tiotropium patients, was 0.14 L above baseline (12% increase) compared to 0.02 L for those in the ipratropium group. The mean FEV_1 trough response following SPIRIVA ranged from 0.12 L-0.14 L over baseline (0.13 L-0.17 L over ipratropium). The mean FEV_1 average response during the first three hours following SPIRIVA ranged from 0.23 L-0.27 L over baseline (0.07 L-0.12 L over ipratropium). SPIRIVA was more effective than ipratropium ($p < 0.05$) at all time points except for the first two hours following the first dose and up to one hour post dose one week later. After one year, trough FEV_1 was 0.12 L above baseline for SPIRIVA patients and had declined 0.03 L for ipratropium patients (difference of 0.15 L between groups, $p < 0.001$).

The FVC response mirrored the FEV_1 response. Mean increase in FVC was 0.32 L over baseline after one year for patients receiving tiotropium and 0.11 L for those receiving ipratropium. The mean FVC average response during the first three hours following SPIRIVA ranged from and 0.50 L–0.57 L over baseline (0.08 L-0.12 L over ipratropium) at steady state. The difference between SPIRIVA and ipratropium was statistically significant ($p < 0.05$).

The TDI showed that SPIRIVA was significantly more effective than ipratropium in reducing dyspnea. TDI focal score between SPIRIVA and ipratropium groups at 9 and 12 months were 0.97 and 0.9, respectively. Also, the proportion of patients who achieved a clinically meaningful difference in TDI focal score (improvement of ≥ 1 unit) at one year was significantly greater in the SPIRIVA group (31%) vs ipratropium (18%; $p = 0.004$).

Additional results included: 1) PEFRs (morning and evening) greater for SPIRIVA compared to ipratropium ($p < 0.01$ at all weekly intervals), 2) exacerbations significantly lower in the SPIRIVA group than in the ipratropium group (35% vs 46% respectively, $p = 0.014$), 3) time to onset of first exacerbation significantly delayed ($p = 0.008$) 4) hospitalizations associated with COPD exacerbations were 7.3% and 11.7% for the SPIRIVA and ipratropium groups ($p = 0.11$), 5) fewer days hospitalized secondary to exacerbations (33% lower) for patients receiving SPIRIVA ($p = 0.09$) 6) improvements in the SGRQ were maintained throughout the year and were superior to ipratropium ($p < 0.05$), 7) SPIRIVA patients used significantly less salbutamol than ipratropium patients ($p < 0.05$ for 40 of the 52 weeks).

- *SPIRIVA vs Salmeterol and Placebo*

A total of 1207 patients (402 receiving SPIRIVA, 405 receiving salmeterol and 400 receiving placebo) were randomized in the six-month trials with equal allocation for SPIRIVA, salmeterol and placebo. A significantly

greater percent of patients in the SPIRIVA group (84.6%) completed all visits compared to those in the placebo group (74.3%; $p<0.05$). A total of 81.2% patients in the salmeterol group completed these trials (Trial A and Trial B); the difference between SPIRIVA and salmeterol or that between salmeterol and placebo was not statistically significant. Also, fewer patients in the SPIRIVA group failed to complete the studies due to worsening of COPD (5.0%) compared to those in the salmeterol group (10.1%) and in the placebo group (11.3%).

At the screening visit, the mean FEV_1 was 1.12 L for the SPIRIVA group, 1.07 L in the salmeterol group, and 1.09 L in the placebo group; 41%, 39%, and 41% of predicted respectively. Screening demographics were balanced amongst the groups. Both Trial A and Trial B conducted spirometry at baseline, randomization and after 2, 8, 16, and 24 weeks of therapy. In both trials spirometry was performed before doses. However, serial spirometric evaluations were performed to 12 hours in Trial A and limited to 3 hours in Trial B. Dyspnea was assessed at baseline with the BDI and changes were recorded with the TDI.

For Trial A, trough FEV_1 was significantly improved over placebo at 24 weeks by 0.137 L in the SPIRIVA group and by 0.085 L in the salmeterol group. Both active drugs improved FEV_1 compared to placebo. The difference between SPIRIVA and salmeterol was significant (0.052 L; $p < 0.01$). And the trough FEV_1 response of SPIRIVA versus salmeterol was statistically significant ($p < 0.05$) on all days except on day 15 and day 57. At the end of the trial the trough, average, and peak FEV_1 response of SPIRIVA versus placebo and versus salmeterol was statistically significant ($p < 0.001$).

For Trial B, the mean trough FEV_1 response of SPIRIVA was up to 0.02L over salmeterol and 0.11L – 0.12L over placebo throughout the 24-week treatment period. The trough, average, and peak FEV_1 response of SPIRIVA versus placebo was statistically significant on all test days ($p < 0.001$). The trough response of SPIRIVA vs salmeterol was numerically greater (0.04L – 0.06L) but not significant at the end of the trial. However, peak and average FEV_1 for tiotropium was superior to salmeterol at the end of the trial.

When the data from the two trials were pooled, the mean FEV_1 trough response of SPIRIVA ranged from 0.12 L-0.13 L over placebo and 0.01 L-0.04 L over salmeterol. The mean FEV_1 average response ranged from 0.20 L-0.21 L over placebo and 0.05 L-0.06 L over salmeterol. The difference between SPIRIVA and placebo was highly statistically significant on all test days in each trial in each FEV_1 endpoint ($p<0.01$).

In each of the two six-month trials the FVC response also followed the FEV_1 response. For Trial A (12-hour spirometry) the trough, peak and average FVC response of SPIRIVA was significant vs salmeterol, whereas in Trial B (3-hour spirometry) only peak and average FVC were significant. When data from both trials were combined the FVC response for trough, peak, and average (3-hour spirometry) were significant. At steady state the mean FVC average response during the first three hours following SPIRIVA ranged from 0.40 L-0.46L over baseline (0.31 L-0.39 L over placebo and 0.04 L-0.14 L over salmeterol). The difference between tiotropium and placebo and that between SPIRIVA and salmeterol was statistically significant ($p<0.05$).

SPIRIVA was shown to be significantly more effective than placebo in reducing dyspnea. For the combined studies, at six months, the TDI focal score, compared to placebo, improved in the SPIRIVA group by 1.1 units ($p<0.001$) and the salmeterol group by 0.7 units ($p<0.05$) with the difference between SPIRIVA and salmeterol groups 0.4 ($p=0.17$). For each trial, SPIRIVA exceeded the minimally clinically meaningful difference of one unit. The percentages of patients who improved their TDI focal score by one or more was 43% for those on SPIRIVA, 41% on salmeterol and 30% on placebo ($p<0.01$ for active treatment compared to placebo).

Additional results included: 1) PEFRs (morning and evening) were greater for both SPIRIVA and salmeterol compared to placebo throughout the 24-week treatment period ($p < 0.01$ for SPIRIVA vs placebo, both morning and evening and $p < 0.05$ SPIRIVA vs salmeterol for evening), 2) SPIRIVA patients experienced fewer COPD exacerbations/patient year compared to placebo ($p = 0.02$), a finding not observed with salmeterol, 3) SPIRIVA delayed the onset of first exacerbation compared with placebo ($p=0.005$) whereas salmeterol did not 4) hospitalizations and number of days hospitalized secondary to COPD exacerbations showed a non-statistically

significant trend for being less for patients treated with SPIRIVA compared to salmeterol and placebo 5) SGRQ total score improved 4.2, 2.8, and 1.5 units over the six-months for the SPIRIVA, salmeterol, and placebo groups, respectively (p <0.01 SPIRIVA vs. placebo).

- *Salmeterol versus SPIRIVA 12 week Trial Summary*

A randomized, double-blind, double-dummy, parallel-group study was conducted to compare daytime bronchodilator efficacy of tiotropium 18 mcg once daily with salmeterol 50 mcg twice daily in patients with COPD. Serial spirometry was performed over 12 hours after 12 weeks of treatment. Co-primary endpoints were average (over 12 hours) and peak FEV_1 at 12 weeks. 608 patients were randomized (308 tiotropium, 300 salmeterol): mean age 64 years; 66% male; mean baseline FEV_1 1.05L (37.7% predicted). After 12 weeks, the average post-dose FEV_1 over 12 hours was significantly higher with tiotropium compared with salmeterol (167 vs. 130 mL, respectively, p=0.03), as was peak FEV_1 (262 vs. 216 mL, respectively, p=0.01). The average FEV_1 responses from 0-6 hours and 6-12 hours were higher in the tiotropium group compared with salmeterol (p<0.05). Peak and average FVC were significantly higher with tiotropium compared with salmeterol (p<0.01). Pre-dose FEV_1 responses were not significantly different; however, tiotropium demonstrated a significantly higher pre-dose FVC than salmeterol (p<0.05). In conclusion, tiotropium demonstrated significantly greater post-dose improvements in spirometric parameters compared with salmeterol. These improvements were sustained over 12 hours. (Briggs DD, et al. *Pulm Pharmacol Ther* 2005; 18:397-404)

Safety

SPIRIVA has been evaluated for safety in over 4,000 patients, including 1,701 patients exposed to the 18 mcg dose (data on file,). Of this number 48% were exposed to the drug for more than 200 days and 34% for more than 330 days.

Discontinuation of therapy due to an adverse event occurred in 9.6% and 13.7% of patients in the one-year tiotropium vs. placebo studies respectively (p < 0.05), 10.1% and 12.8% in the one-year SPIRIVA vs ipratropium studies (p = 0.089), and in 7.2% of patients receiving SPIRIVA in the six-month trials compared to salmeterol (14.8%) and placebo (16.0%) (p =0.01 SPIRIVA vs. placebo and p=0.01 SPIRIVA vs. salmeterol). Overall, the most frequently reported adverse event in all patients treated with SPIRIVA was dry mouth, including dry throat (16% of patients in the placebo-controlled trials, 12% in the ipratropium-controlled trials, and 8.2% in the six-month trials). In general, dry mouth was mild to moderate and had a median onset of three to five weeks in the one-year studies and 15 days during the six-month studies. Dry mouth often resolved during continuation of therapy.

Adverse events reported by 3% or more of patients in the SPIRIVA 18mcg group in either the one year placebo-controlled or one year ipratropium-controlled trials are presented in Table 1. Frequent events (≥3%) with a consistently higher incidence (by at least 1%) in both SPIRIVA groups compared to their control groups were chest pain, dry mouth, pharyngitis, sinusitis, moniliasis, upper respiratory tract infections, and urinary tract infections. In the placebo-controlled trials constipation and rash were also reported more frequently in the SPIRIVA group, however, this was not seen in the one year ipratropium-controlled trails. Arthritis, coughing, and influenza-like symptoms occurred at a rate of ≥3% in the SPIRIVA treatment group, but were <1% in excess of the placebo group.

Other events that occurred in the SPIRIVA group at a frequency of 1% to 3% in the placebo-controlled trials and where the rates exceeded that in the placebo group include: *Body as a Whole:* allergic reaction, leg pain; *Central and Peripheral Nervous System:* dysphonia, paraesthesia; *Gastrointestinal System Disorders:* gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders:* hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders:* skeletal pain; *Cardiac Events:* angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder:* depression; *Resistance Mechanism Disorders:* herpes zoster; *Respiratory System Disorder (Upper):* laryngitis;

Vision Disorder: cataract. In addition, among the adverse events observed in the clinical trials with an incidence of <1% were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age.

Two multicenter, 6-month, controlled studies evaluated SPIRIVA in patients with COPD. The adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.

The following adverse reactions have been identified during worldwide post-approval use of SPIRIVA: dizziness, epistaxis, hoarseness, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

Table 1. Adverse Experience Incidence (% Patients) in One-Year COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA [n=550]	Placebo [n=371]	SPIRIVA [n=356]	Ipratropium [n=179]
Body as a Whole				
Accidents	13	11	5	8
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Musculo-Skeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (upper)				
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Sinusitis	11	9	3	2
Upper Respiratory Tract Infection	41	37	43	35
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Legend for Table 1

[a] Accidents–Includes accidents household, accidents vehicular and falls

[b] Edema, dependent–Includes oedema, oedema dependent, oedema generalized, oedema legs, oedema peripheral

[c] Hypertension–Includes hypertension and hypertension aggravated

[d] Arthritis–Includes arthritis, arthritis aggravated, arthralgia and arthrosis

[e] Infection–Includes infection, infection bacteria and infection viral

[f] Moniliasis–Included moniliasis and moniliasis genital

[g] Rash–Includes rash, rash erythematous and rash maculo-papular

[h] Urinary Tract Infection-Includes urinary tract infection and cystitis

Percentages are calculated using total number of patients treated as the denominator

Pooled Clinical Trial Analysis of Tiotropioum Safety

Kesten S, et al conducted a retrospective safety analysis for tiotropium. (Chest 2006;130:1695-1703) Data was pooled on adverse events from 19 randomized, double-blind, placebo-controlled trials with tiotropium in patients with COPD (17 studies) and asthma (2 studies) using data available as of May 2004. Heterogeneity of incidence rate ratios was examined by trial prior to pooling. Incidence rates of selected adverse events and Maentel-Haenszel incidence rate ratio estimates were computed, and 95% confidence intervals were used for precision of effect estimates. Patients were included in the study until 30 days post-treatment (tiotropium, placebo) or until they had the event of interest, whichever came first.

The pooled population included 7,819 patients (4,435 tiotropium; 3,384 placebo), contributing 2,159 person-years of exposure to tiotropium and 1,662 person-years of exposure to placebo. Dyspnea, dry mouth, COPD exacerbation and upper respiratory tract infection were the most common events. There was a decreased relative risk of dyspnea (RR = 0.64, 95% CI = 0.05, 0.81) and COPD exacerbation (RR = 0.72, 95% CI = 0.64, 4.11). Serious cardiac conditions, such as cardiac arrest and myocardial infarction did not occur more frequently with tiotropium. There was an elevated risk of urinary retention (RR = 10.93, 95% CI = 1.26, 94.88). There was a lower risk of all cause mortality (RR = 0.76, 95%CI = 0.50, 1.16), cardiovascular mortality (RR = 0.57, 95% CI = 0.26, 1.26) and respiratory mortality (RR = 0.71, 95%CI = 0.29, 1.74) with tiotropium.

The benefit/risk profile is characterized by decreased risk of dysnea and COPD exacerbation and increased risk of dry mouth and urinary retention. Pooling of adverse event data from preapproval and postapproval clinical trials increases the precision of effect estimates and is consistent with the present safety profile of tiotropium.

Asthma Therapy

Tiotropium Use in Asthma Patients

Boehringer Ingelheim Pharmaceuticals, Inc. conducted four Phase II clinical trials to evaluate the potential benefits of tiotropium in patients with asthma.[1-4] These studies varied in design, tiotropium dose, inhalation delivery device used, and end point measurements. The four studies are summarized below; results were mixed and treatment was well tolerated. Of note, SPIRIVA is not indicated for the management of asthma and is only available as an 18.0 μg powder capsule for inhalation through the HandiHaler® inhalation device.

O'Connor et al. conducted a randomized, double-blind, single dose, four-way, crossover trial in 12 male asthmatic patients (mean age of 26 years) to determine the effects of single-dose tiotropium (10, 40, and 80 μg) administered by dry powder inhalation compared with placebo against methacholine-induced bronchoconstriction. On each study day (four separate occasions 11-24 days apart) serial methacholine challenges (at 2, 12, 24, 36 and 48 hours post drug) were performed until a PC_{20} [provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second (FEV_1)] was achieved. Tiotropium produced a dose-dependent protection against methacholine challenge for up to 48 hours and at two hours (the peak effect) the protective effect of tiotropium was 5.0 ± 1.1, 7.1 ± 0.5, and 7.9 ± 0.7 (mean ± SEM) doubling doses after 10, 40, and 80 μg respectively. These single doses of tiotropium also produced bronchodilation; an increase in FEV_1 of 5.5 – 11.1% from baseline that was maintained for 24 hours, however, at 36 and 48 hours after drug administration the variability in FEV_1 did not differ significantly from placebo. Dosing with tiotropium was well tolerated by all patients; the most commonly observed adverse events were coughing and nocturnal exacerbations of asthma.

Noveck et al. evaluated the safety and efficacy of tiotropium (4.5, 9.0, 18.0, and 36.0 μg) vs. placebo in moderate to severe asthmatics. Two-hundred-and-four patients (mean age of 39 years) were randomized to receive either placebo (n=40), 4.5 μg (n=42), 9.0 μg (n=42), 18.0 μg (n=40), or 36.0 μg (n=40) of tiotropium once daily, administered by dry powder inhalation via the HandiHaler. During this three-week, double-blind, parallel group trial tiotropium (at all four doses) produced a statistically significant increase in FEV_1 up to four hours after dosing compared to placebo ($p < 0.05$). The FEV_1 response was not dose dependent; all doses of tiotropium induced an approximately similar increase in FEV_1. In all dosing groups, the peak bronchodilative effect was observed approximately two hours post dosing with an absolute increase in FEV_1 corrected for placebo of 254, 300, 350, and 296 ml after dosing with 4.5, 9.0, 18.0, and 36.0 μg respectively. However, the 24-hour post dosing (trough effect) was not significant. Dry mouth and headache were the most commonly observed adverse events with a dose-related incidence in dry mouth.

In a four-week, double-blind, double-dummy, parallel group, placebo and active-controlled trial, tiotropium failed to show meaningful efficacy in patients with nocturnal asthma when compared to placebo (data on file). Two-hundred-and-twenty-four patients (mean age of 38 years) with well-defined nocturnal asthma were randomized to receive either tiotropium [4.5 μg (n=37), 9.0 μg (n=36), 18.0 μg (n=37), or 36.0 μg (n=35)] inhalation powder capsules once daily via the HandiHaler, salmeterol inhalation aerosol (50 μg/bid, n=40), or placebo (n=39). Four weeks of treatment with tiotropium had no effect on morning peak expiratory flow rate (PEFR), the number of awakenings, or patient symptoms. In comparison, treatment with salmeterol resulted in improvement of nocturnal asthma as assessed on several time-points. Reported adverse events were equally distributed across all six-treatment groups with headache and upper respiratory tract infection as the most frequent events.

Lastly, Richter et al. conducted a randomized, double-blind, placebo-controlled, parallel group trial over 21 days to determine the protective effect and safety of 36 μg tiotropium on exercise-induced bronchospasm (EIB) and against methacholine challenge in patients with asthma. Thirty-one patients (mean age of 32.4 years) with stable bronchial asthma were enrolled from one center and inhaled study drug each morning through the HandiHaler. Responses were evaluated on day one and day 21 at six and 24 hours post treatment. Tiotropium did not significantly protect against EIB, with the mean maximum decrease in FEV_1 after exercise reported as –0.95, -0.71, -1,44, -0.66 L for tiotropium and –0.97, -0.82, -1.26, and –1.02 L for placebo at the different time points. Tiotropium treatment resulted in consistent protection against methacholine-induced bronchoconstriction compared to placebo and

protection was maintained throughout the entire study period up to 24-hours after inhalation of the last dose (p=0.0001). Treatment was well tolerated with headache the most frequently reported adverse event.

In summary, the four trials described above reveal mixed results with modest efficacy at best. Treatment was generally well tolerated with the most common adverse events being asthma exacerbation, upper respiratory infection, headache, and dry mouth. Boehringer Ingelheim Pharmaceuticals, Inc. does not recommend the use of SPIRIVA in the treatment or management of asthma.

Tiotropium Use in COPD Patients with Asthma

Mangussen et al. performed a 12-week randomized, double-blind, placebo-controlled, parallel group trial with tiotropium 18 mcg daily. The primary objective of the trial was to demonstrate the superiority of tiotropium 18 mcg once daily administered via the HandiHaler compared to placebo in the treatment of patients with COPD and a concomitant diagnosis of asthma. The primary efficacy endpoint was the change in FEV_1 $AUC_{0\text{-}6h}$ after 12 weeks of treatment. Patients were allowed to continue usual respiratory medications except for inhaled anticholinergics. Participation was contingent upon the following inclusion criteria: diagnosis of both COPD and asthma, age $\geq$40 years, smoking history >10 pack years, post-bronchodilator FEV_1<80% predicted, FEV_1/FVC<70%, $\geq$12% and $\geq$200 ml increase in FEV_1 following inhaled bronchodilator at the screening visit or documented within the last 5 years in patient's records, and received inhaled steroids $\geq$1 year prior to study entry. At baseline and 4 and 12 weeks following randomization, spirometry was measured 30 and 10 minutes before the study drug administration and serially for 6 hrs post-dosing. Four hundred seventy two patients were randomized to tiotropium 18 mcg (228 patients) or matching placebo (244 patients). The mean age of the patient population was 59.6 years, 61.4% men, and the mean FEV_1 was 1.55 L (53.0% predicted). The mean duration of COPD and asthma was 9.2 and 43.2 years, respectively. Baseline characteristics of the two treatment groups were balanced. At 12 weeks, improvements were noted in the primary endpoint (FEV_1 $AUC_{0\text{-}6h}$ difference 186±24 ml, p<0.001) and for morning pre-dose FEV_1 (difference 98±23 ml, p<0.001). Further, significant differences in favor of tiotropium were observed for pre-dose FVC (difference 128±34 ml, p<0.001) and FVC $AUC_{0\text{-}6h}$ (difference 232±35 ml, p<0.001). Compared to baseline, the mean weekly number of daily puffs of rescue salbutamol was significantly decreased in the tiotropium arm (difference between placebo and tiotropium groups of 0.45±0.17 puffs, p<0.05). Of 472 randomized patients, 176 (37.3%) reported adverse events during the treatment period with similar frequency in the active and placebo arms. The most frequent adverse events were lower respiratory system disorders (placebo: 20.1%; tiotropium 12.7% with exacerbations being the most commonly reported), upper respiratory system disorders (placebo: 5.7%; tiotropium: 13.2%), and gastrointestinal system disorders (placebo 5.7%; tiotropium 9.6%, with dry moth being reported most commonly). The frequency of COPD exacerbations was lower in the tiotropium arm (5.7% versus 10.7% in the placebo arm) and the frequency of asthma was similar in the groups (placebo: 3.3%; tiotropium 2.6%). The investigators concluded that tiotropium is safe and effective in patients with COPD and concomitant asthma (observed spirometric improvements along with symptomatic benefit as evidenced by decreased use of rescue salbutamol). However, whether tiotropium was only treating the COPD component or had some effect on the concurrent asthma could not be discerned.

References:

1. O'Connor BJ et al. Prolonged effect of tiotropium bromide on methacholine-induced bronchosonstriction in asthma. *Am J Respir Crit Care* 1996;154:876-880.
2. Noveck R et al. Bronchodilator effect of tiotropium in moderate-severe asthmatics. *Am J Respir Crit Care Med* 1999;159:A625.
3. Data on File, Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT, 9 November 1998.
4. Richter K et al. Effect of acute and chronic treatment with a long-acting anticholinergic agent (tiotropium) on airway responsiveness in asthmatics. *Eur Respir J* 1999;14(Suppl 30):288S.
5. Mangussen H et al., Improvements with tiotropium in COPD patients with asthma. *Respiratory Medicine.* 2008;102:50-56.

Combined with Inhaled Corticosteroids

COPD treatment guidelines recommend initial treatment with inhaled bronchodilators. In addition to bronchodilator therapy, inhaled steroids are often prescribed in patients with COPD despite modest evidence for effectiveness of inhaled steroids in a subset of COPD patients. Tiotropium is a once daily-inhaled anticholinergic for the treatment of COPD that has its effect through prolonged M3-receptor antagonism. Hodder, et al. sought to determine the benefits of combination therapy using tiotropium 18 mcg once daily vs. salmeterol 50 mcg bid by retrospectively reviewing two 6-month placebo-controlled trials in patients with COPD. Patients were randomly assigned to tiotropium, salmeterol or placebo. The analysis was based on combining the trials and only examining patients treated with inhaled steroids prior to randomization. Mean FEV1 in this subgroup was 1.08 liters in the tiotropium group (n = 253) and 1.04 liters in the salmeterol group (n = 271). Morning pre-dose (trough) improvement in FEV_1 at 6 months was 73 ml (tiotropium) vs. 46 ml (salmeterol). Trough improvement in FVC at 6 months was 173 ml (tiotropium) vs. 89 ml (salmeterol). Compared to placebo, mean transition dyspnea index focal score was higher with the tiotropium combination (1.04 units) but not with the salmeterol combination (0.57 units). In addition, compared to placebo, the number of exacerbations for the combination was reduced with tiotropium but not with salmeterol. Changes at 6 months in SGRQ total score relative to placebo were 3.30 (tiotropium) and 1.27 (salmeterol). In summary, in this post-hoc analysis of COPD patients receiving inhaled steroids in 6 month clinical trials, tiotropium provided benefits over salmeterol in lung function, dyspnea, exacerbations, and quality of life.

Reference:

Hodder H et al. Outcomes in COPD patients receiving tiotropium or salmeterol plus treatment with inhaled corticosteroids. *International Journal of Chronic Obstructive Pulmonary Disease.* 2007; 2(2):1-11

Hyperinflation

Hyperinflation, which occurs at rest and worsens with exercise, is a physiological abnormality that is commonly seen in patients with chronic obstructive pulmonary disease (COPD). It is manifested primarily by an increase in functional residual capacity (FRC) and a decrease in inspiratory capacity (IC). This condition can lead to restrictions in tidal volume expansion during activity and also places the muscles of respiration at a mechanical disadvantage. Hyperinflation increases the work of breathing, worsens with exercise, and therefore reduces exercise tolerance (dynamic hyperinflation). Inhaled bronchodilators improve dynamic hyperinflation, as well as hyperinflation at rest (static hyperinflation), thereby reducing the work of breathing and increasing exercise tolerance.[1]

Numerous clinical studies and reviews have shown an improvement in the reduction of hyperinflation with the use of inhaled tiotropium (SPIRIVA) in patients with chronic obstructive pulmonary disease (COPD). [2-7]

Celli et al. evaluated the effect of SPIRIVA 18mcg daily on inspiratory capacity (IC) in a 4-week, randomized, double-blind, placebo-controlled study conducted in 81 patients with stable COPD. The mean age of the subjects was 63 years old, 62% were men, and mean baseline forced expiratory volume in 1 second (FEV_1) was 1.12L (43% of predicted). At each of the visits (weeks 0, 2 and 4) FEV_1, forced volume capacity (FVC), IC, slow vital capacity (SVC), and thoracic gas volume (TGV) or functional residual capacity (FRC) were measured prior to study drug (-60min and -15min) and after study drug (30 min, 60 min, 120 min, and 180 min). The percentage improvement in area under the curve above baseline with SPIRIVA was similar among FEV_1 and lung volumes (FEV_1 18%; FVC 20%; SVC 16%; IC 16%; FRC 14%). Observed improvements in IC and reductions in TGV or FRC with once daily SPIRIVA reflect improvements in hyperinflation that are maintained over 24 hours.[2]

In a 12-week multicenter, randomized, double-blind comparison of once-daily inhaled SPIRIVA (N=46) with placebo (N= 54), SPIRIVA showed significant decrease in lung hyperinflation as measured by forced volume capacity (FVC), inspiratory capacity (IC), and slow vital capacity (SVC). The improvement in both spirometric measurements, FVC (trough and peak) and IC (trough and peak) can be shown on figure 1 and figure 2, respectively. Compared to placebo, SPIRIVA has induced greater improvement in the peak SVC. In addition, airway obstruction was also improved in the SPIRIVA group, compared to the placebo group. This was demonstrated by significant improvements in Forced Expiratory Volume in the first second (FEV1) and peak expiratory flow rate (PEFR) [$p < 0.05$, respectively for all measures]. In addition, SPIRIVA provided a measurable improvement in exercise capacity and dyspnea. At the end of the trial, patients in the SPIRIVA group had a consistent and clinically significant improvement in their health-related quality of life (HRQoL), which was measured by the St. George's Respiratory Questionnaire (SGRQ) total score ($p < 0.05$ vs placebo). [3]

Figure 1: Mean trough (a**,** predose) and peak (b, postdose) FVC. Adjusted means (± 2 SE) are shown (* $p < 0.05$, ** $p < 0.001$ vs. placebo).[3]

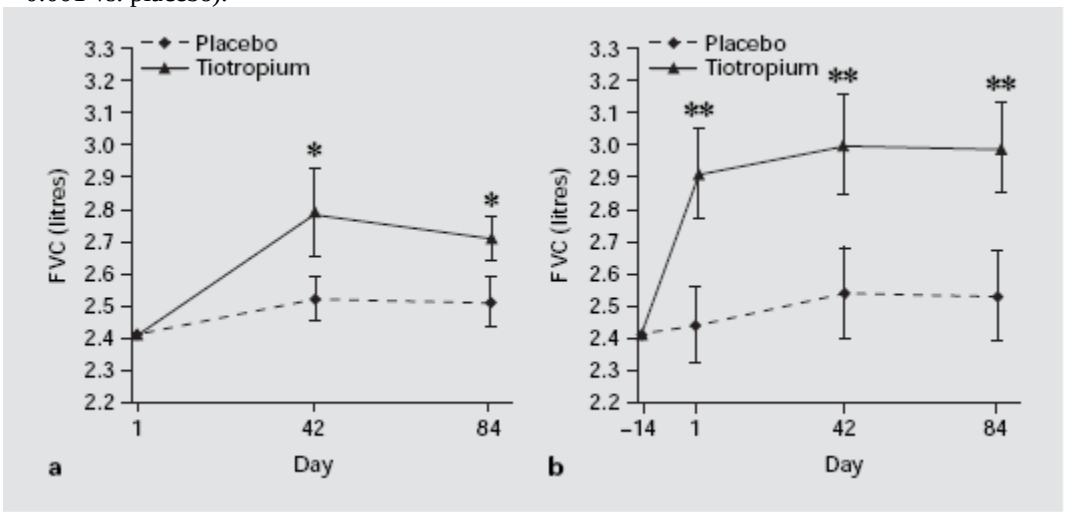
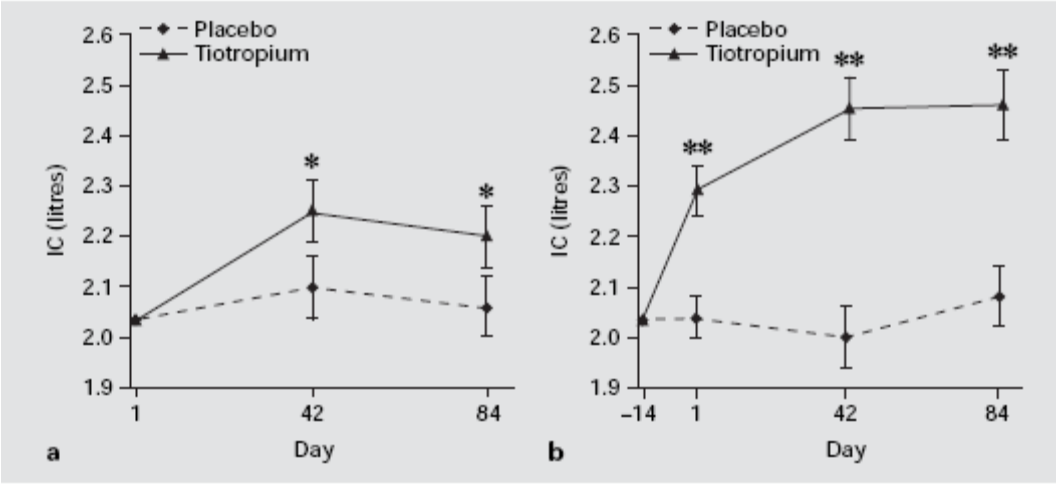


Figure 2: Mean trough (a**,** predose) and peak (b, postdose) IC. Adjusted means (± 2 SE) are shown (* p <0.05, ** p < 0.001 vs. placebo). [3]



A review article by Cooper described how hyperinflation of the lungs reduces IC, not only at rest (static hyperinflation) but also during physical activity (dynamic hyperinflation). The article also reviewed the evidence on the effects of bronchodilators (such as SPIRIVA) on hyperinflation, exercise endurance, and dyspnea in patients with chronic obstructive pulmonary disease (COPD).[4] The data on SPIRIVA are summarized in table 1. The author concluded that bronchodilators such as SPIRIVA can reduce airway resistance and ventilatory requirements during exercise. These changes can lead to an improvement in IC, which is indicative of reduced hyperinflation. Also, the improvement in IC was associated with a significant reduction in dyspnea and increased exercise tolerance.

Table1[4]:

Bronchodilator	Study	Year	N	Baseline FEV1 (%)	Increase in Static IC* (mL)	Increase in Dynamic IC† (mL)	Increase in Exercise Endurance	Change in Dyspnea	*P* Value
SPIRIVA	Celli et al[2]	2003	81	43	350	NM	NM	NM	<0.01 vs. placebo
	O'Donnell et al[5]	2004	187	44	230	180	105 sec	↓II	<0.05 vs. placebo
	Maltais et al[6]	2005	261	43	220 150	220 140	235 sec 171 sec	↓II ↓II	<0.01 vs. placebo¶ <0.01 vs. placebo#

FEV_1 =forced expiratory volume in 1 second; IC = inspiratory capacity; NM = not measured
*IC measured during body plethysmography as total lung capacity (TLC) minus functional residual capacity.
†IC measured at isotime during constant load submaximal exercise.
II Dyspnea reduced at isotime.
¶ Measured 8 hours after dosing.
# Measured 2.25 hours after dosing.

Another review article by Casaburi discussed several interventions that can reduce hyperinflation during exercise. These interventions are bronchodilator therapy, inhalation of supplemental oxygen or a helium/oxygen mixture, and rehabilitative exercise programs. The article suggested that the combinations of rehabilitative exercise training with supplemental oxygen, or with SPIRIVA, have been found to yield additive effects on reducing dynamic hyperinflation and that subsequently can improve the mobility of COPD patients.[7]

A study by Gelb AF, et al.[8] was conducted in 60 patients with moderate to severe COPD to detect dynamic hyperinflation (DH) by measuring the reduction in inspiratory capacity (IC) during metronome-paced hyperventilation (MPH) studied before and after treatment with tiotropium. A reduction in IC during exercise is a reflection of DH and is a good predictor of exertional dyspnea and decreased exercise ability in COPD patients. In a previous study, Gelb AF, et al.[9] compared MPH, a relatively simple procedure, with incremental symptom-limited cycle ergometry to induce a respiratory rate induced DH and decreased IC in patients with moderate to severe COPD and reported similar changes in IC. This later study evaluated the role of tiotropium in MPH-induced DH. At basline 80% of the patients were tiotropium naïve and 20% had a 30-day washout time. Patients had a smoking history of >20 pack-years, were stable for at least 6 weeks prior to the study and were not receiving oxygen. Twenty-eight of the 60 patients were men and the mean age was 66 ± 10 years. IC and FEV_1 were measured before and immediately after MPH at two times the resting respiratory rate for 20 seconds before and after 30 days of treatment with tiotropium bromide 18mcg daily. Patients were encouraged to maintain a constant tidal volume during MPH.

At baseline FEV_1 was 1.5 ± 0.1 L, mean FVC was 2.6 ± 0.1 L, and mean FEV_1/FVC was 56 ± 1%. Compared to baseline, after 30 days and 1.5hr after tiotropium dose there was an increase in IC of 0.18 ± 0.04L ($p<0.0001$); FEV_1 of 0.13 ± 0.03L ($p=0.0002$); FVC of 0.22± 0.05L ($p<0.001$); and decrease in end-expiratory lung volume (EELV)/total lung capacity (TLC) of -3.1 ± 0.6% ($p=0.0001$); a decrease in end-inspiratory lung volume (EILV)/TLC of -2.9 ± 1.3% ($p=0.03$); and no change in TLC. Results following MPH-induced DH at baseline and after 30 days of tiotropium were similar, with decreases in IC (-0.35 ± 0.03L; $p<0.001$); FEV_1 (-0.05 ± 0.04L ($p=0.2$); FVC (-0.22 ± 0.03L ($p<0.0001$); no change in TLC; and increases in EELV/TLC (11.8 ± 1% of predicted, $p<0.0001$) and EILV/TLC (4.0 ± 1.3% of predicted, $p<0.003$). In conclusion, in patients with moderate to severe COPD, tiotropium did not reduce the degree of MPH-induced DH and reduction in IC, compared to baseline. However, the bronchodilatory effects of tiotropium which increased the baseline IC, lowered the operational lung volumes and may "volume-protect" against DH. Hence patients had a significantly greater IC after MPH when treated with SPIRIVA, compared to the previous measurements prior to SPIRIVA treatment.. MPH is noninvasive and simple to administer, and thus provides a clinically useful method to monitor changes in IC following tiotropium.

References:

1. ER Sutherland, RM Cherniack. Management of chronic obstructive pulmonary disease -current concepts. *NEJM* 2004; 350: 2689-97.
2. B Celli, R ZuWallack, S Wang, et al. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in chronic obstructive pulmonary disease patients with increased static lung volumes. *Chest* 2003;124:1743–1748.
3. C Verkindre, F Bart, B Aguilaniu et al. The effect of tiotropium on hyperinflation and exercise capacity in chronic obstructive pulmonary disease. *Respiration* 2006; 73:420-427.
4. CB Cooper**.** The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. *The American Journal of Medicine* 2006; 119 (10) Suppl1: 21-31.
5. DE O'Donnell DE, T Fluge , F Gerken , et al. Effects of tiotropium on lung hyperinflation, dyspnea and exercise tolerance in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2004;23:832–840.
6. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptoms limited exercise performance over 8 h with once-daily tiotropium in patients with chronic obstructive pulmonary disease. *Chest* 2005;128:1168 –1178.
7. R Casaburi, J Porszasz. Reduction of hyperinflation by pharmacologic and other interventions**.** *Proc Am Thorac Soc* 2006; 3:185-189.
8. Gelb AF, Taylor CF, McClean PA, et al. Tiotropium and simplified detection of dynamic hyperinflation. Chest 2007;131:690-695.
9. Gelb AF, Gutierrez CA, Weisman AM, et al. Simplified detection of dynamic hyperinflation. Chest 2004;126:1855-1860.

Use in Patients Previously Naïve to Maintenance Therapy

The current guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommend the routine use of long acting bronchodilators as maintenance therapy in patients with GOLD stage II or greater.[1] Despite this, patients with symptomatic COPD may not prescribed maintenance therapy. Data regarding the efficacy of long acting bronchodilators when introduced to the treatment regimen of patients previously naïve to maintenance therapy is limited.

Adams et al.[2] evaluated the efficacy of SPIRIVA in patients with COPD who were not previously taking maintenance therapy in a post-hoc analysis of data from two 1-year randomized double-blind, placebo-controlled tiotropium trials.[3] The objectives of this analysis were to determine whether SPIRIVA once daily improves lung function and symptoms in "undertreated" COPD patients (*N=218*).

In this analysis, "undertreated" COPD patients were defined as those who were not previously treated with maintenance respiratory medications at the time of study enrollement.[2,3] These COPD patients were characterized as follows :

- Those who had not been treated before with maintenance respiratory therapy (*N=178*); or
- Those who were treated only with as-needed (PRN) short acting β_2-agonist (albuterol) therapy (*N=40*)

These "undertreated" COPD patients (N=218) were allocated to receive either SPIRIVA (N=130) or placebo (N=88).

The lung function was assessed during this study by examining the trough and peak FEV_1 and FVC post each treatment. Other respiratory outcomes were also measured including, dyspnea (assessed by TDI [Transition Dyspnea Index] Focal score) and health status (assesses by SGRQ [St. George's Respiratory Questionnaire] total score).

The mean trough FEV_1 was 190 mL greater and the mean FVC was 400 mL greater for the SPIRIVA group than for the placebo group at the end of the 1 year study period. The difference in mean peak FVC was 540 mL larger in patients who received SPIRIVA than those who received placebo at the end of the study. "Undertreated" patients who received SPIRIVA had significantly higher mean trough FEV_1 and FVC and peak FEV_1 and FVC, between day 8 and day 344, compared with those who received placebo ($P < 0.001$ for all measured parameters). Both dyspnea (assessed by TDI Focal score) and heath status (assessed by the SGRQ Total score) improved significantly in SPIRIVA treated patients compared to placebo treated patients, these scores were 0.89 and -5.2 , respectively ($P < 0.05$ for both outcomes). The mean use of PRN albuterol during the treatment period of the study was reduced by 0.6 doses/day with SPIRIVA and was increased by 0.4 doses/day with placebo ($P = 0.0007$).[2,3]

In addition, significant clinical benefits in lung function and health status were identified among two subset groups of ''undertreated'' patients, those with the lowest baseline lung function ($FEV_1 < 50\%$) and those whose FEV_1 improved to > 80% on day 8 after treatment with SPIRIVA.[2,3]

Only 19 % (N=25) of SPIRIVA patients and 26% (N=23) of placebo patients discontinued the trial early. Reasons for discontinuation the trial were as followings: worsening of COPD or other pre-existed condition other than COPD, consent withdrawal, lack of efficacy, lost follow up, or other reasons.[2,3]

The authors concluded that SPIRIVA once daily can provide significant improvement in lung function, dyspnea, and health status when given to COPD subjects who previously had not been treated with maintenance therapy for COPD.[2]

As of March 2007, the SPIRIVA is indicated as maintenance treatment for COPD and SPIRIVA is not indicated for initial treatment of acute episodes of bronchospasm, i.e. rescue therapy.[4]

References:

1. Guidelines: global initiative for chronic obstructive lung disease (GOLD) executive summary; Global Strategy for the Diagnosis, Management, and Prevention of COPD. Available at: www.goldcopd.com. Accessed March 20, 2007.
2. Adams SG, Anzueto A, Briggs Jr DD. et al. Tiotropium in COPD patients not previously receiving maintenance respiratory medications. *Respiratory Medicine* 2006;100:1495–1503.
3. Casaburi R, Mahler DA, Jones PW et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary diesease. Eur Respir J 2002;19:217-224.
3. *SPIRIVA* HandiHaler® (tiotropium bromide inhalation powder) [product information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc., August 2006.

Salmeterol Plus Fluticasone Combined with SPIRIVA

A publication in the Annals of Internal Medicine reviewed the results of the Canadian OPTIMAL trial where the combination of tiotropium with salmeterol or fluticasone-salmeterol was compared to tiotropium alone in improving moderate to severe COPD. The study by Aaron SD et al. was a randomized, double-blind, placebo-controlled trial conducted from Oct 2003 to January 2006 at 27 academic and community medical centers in Canada. 449 patients with moderate to severe COPD participated receiving 1 year of treatment with tiotropium with placebo, tiotropium with salmeterol, or tiotropium with fluticasone-salmeterol. The primary endpoint was the proportion of patients who experience a COPD exacerbation that required treatment with systemic steroids or antibiotics.[1]

The proportion of patients in the group that received tiotropium plus placebo who experienced an exacerbation (62.8%) did not differ from that in the tiotropium plus salmeterol group (64.8%; difference, -2 percentage points[95% CI, -12.8 to 8.8 percentage points] or the tiotropium plus fluticasone-salmeterol group (60.0%; difference, 2.8 percentage points [CI, -8.2 to13.8 percentage points]. In sensitivity analyses, the point estimates and 95% confidence bounds shifted in the direction favoring tiotropium plus salmeterol and tiotropium plus fluticasone-salmeterol. In analyses of secondary endpoints, tiotropium plus fluticasone-salmeterol improved lung function (p=0.049) and disease-specific quality of life (p=0.01) and reduced the number of hospitalizations for COPD exacerbations and all-cause hospitalizations compared with tiotropium. In contrast, tiotropium plus salmeterol did not statistically improve lung function or hospitalization rates compared with tiotropium plus placebo.[1]

A limitation of the study was that more than 40% of patients who received tiotropium and tiotropium plus salmeterol discontinued therapy prematurely, and many crossed over to treatment with open-label inhaled steroids or long-acting beta-agonists.[1]

Adding fluticasone-salmeterol to tiotropium therapy did not statistically influence the incidence of COPD exacerbations but did improve lung function, quality of life, and hospitalization rates in patients with moderate to severe COPD.[1]

A pilot, double-blind, double-dummy, randomized, parallel group design trial to assess feasibility of adding an inhaled corticosteroid to two long-acting bronchodilators was conducted by Cazzola et al.[2] Ninety patients with well-controlled COPD were enrolled into the trial. Inclusion criteria required age of 50 or older, current smoking status or a smoking history of at least 20 pack-years, a baseline FEV_1 of less than 50% predicted, and a post-bronchodilator $FEV_1/FVC < 70\%$ predicted. Exclusion criteria were as follows: current evidence of asthma as primary diagnosis, unstable respiratory disease requiring oral/parenteral corticosteroid within 4 weeks prior to beginning the trial, upper or lower respiratory tract infection within 4 weeks of the screening visit, unstable angina or unstable arrhythmias, concurrent use of medications that affect COPD, and evidence of alcohol abuse. At the end of the 2-week run-in period, during which pre-trial COPD treatments (with the exception of stable theophylline regimens) were stopped, patients were randomized into one of three treatment arms: (1) fluticasone/salmeterol 500/50 μg combination (FSC), (2) tiotropium 18 μg, or (3) FSC 500/50 μg + tiotropium 18 μg.

After 4, 8, and 12 weeks of therapy, patients returned to the clinic for study visits. Trough FEV_1 and FVC values were measured, changes in the perception of dyspnea were assessed (through use of bipolar visual anagogic scale [VAS]), and use of supplemental salbutamol was monitored. The primary efficacy measure was the mean change from baseline in pre-dose FEV_1 after 3-month treatment. Secondary efficacy endpoints included change from baseline in VAS score and the use of supplemental salbutamol.

Eighty-one patients completed the trial (26 in the FSC arm, 26 in the tiotropium arm, and 29 in the FCS + tiotropium arm). At baseline, there were no significant ($p<0.05$) spirometric differences between the three treatment groups. After 1 month, significant increases in trough FEV_1 values were observed in all three groups (117mL in FSC, 74mL in the tiotropium, and 115mL in the FSC + tiotropium arm). The difference between the FEV_1 improvements in the FSC and tiotropium arms and that between the tiotropium and the FSC + tiotropium arms was statistically significant, whereas the difference between the FSC and the FSC + tiotropium arms was not. At the end of the trial,

FEV_1 values were improved above baseline by 140mL, 141mL, and 186mL in the FSC, the tiotropium, and the FSC + tiotropium arm, respectively. All three increases reached statistical significance. The difference between the improvements in the FSC and tiotropium groups was not statistically significant; however, the differences between the improvements in the FSC + tiotropium and the mono-component arms were statistically significant. At the end of the treatment, tiotropium and FSC + tiotropium arms showed greater improvements in dyspnea (measured by VAS score) than those observed in the FSC arm. All of the improvements were statistically significant when compared to the baseline, but not significant when compared to one another. The daily use of salbutamol was significantly lower during the treatment period than the 2-week run-in, but similarly to the VAS scores, the differences between the three treatment groups were not statistically significant. Nonetheless, FSC + tiotropium group required fewer puffs of salbutamol than the mono-component groups. The investigators noted that the trial was likely underpowered to detect statistically significant differences in the VAS scores and the use of salbutamol between the three treatment groups. They pointed out, however, that a trial in a larger patient population would potentially find these differences to be statistically significant.

References:

1. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease, A randomized trial. *Ann Intern Med 2007*;146:545-555.
2. Cazzola M, Andò F, Santus P, et al. A pilot study to assess the effects of combining fluticasone proprionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. *Pulm Pharmacol Ther* 2007;20(5):556-561.

INSPIRE Trial

INSPIRE (**I**nvestigating **N**ew **S**tandards for **P**rophylaxis **i**n **R**educing **E**xacerbations) was a 2-year multicenter, randomized, double-blind, double-dummy controlled trial. Before randomization, patients discontinued all existing COPD maintenance medications and received oral prednisolone 30 mg/day along with inhaled salmeterol 50 mg twice daily for 2 weeks (run-in period) to standardize their clinical condition. Qualifying patients were randomized to inhaled salmeterol 50 mg plus fluticasone propionate 500 mg combination (SFC) twice daily by Diskus or tiotropium bromide 18 mg once daily via HandiHaler. After randomization, in addition to study medication, patients were allowed short-acting inhaled beta-agonists as rescue therapy and standardized short courses of oral systemic corticosteroids and/or antibiotics as needed for treatment of COPD exacerbations. Details of any COPD exacerbations, unscheduled health care visits, and adverse events were recorded at 2, 8, and every 12 weeks thereafter. Post-dose FEV_1 and other respiratory parameters were measured at weeks 2 and 8, and every 24 weeks thereafter with St. George's Respiratory Questionnaire (SGRQ) collected at weeks 32, 56, 80, and 104.

The inclusion criteria were as follows: patients aged 40 to 80 years with a smoking history of 10 or more pack-years, a clinical history of COPD exacerbations, a post-bronchodilator FEV_1 of less than 50% predicted, reversibility to 400 mg salbutamol 10% or less of predicted FEV_1, and a score of 2 or more on the Modified Medical Research Council dyspnea scale. Patients with any respiratory disorder other than COPD or who required daily long term oxygen therapy (>12 h/d) were excluded from the trial.

The primary efficacy endpoint was the rate of health care utilization (HCU) exacerbations. These were defined as requiring treatment with oral corticosteroids and/or antibiotics or requiring hospitalization. Secondary endpoints included health status measured using SGRQ, post-dose FEV_1, which was measured 2 h after inhalation of study medication, and withdrawal rate from the trial. All-cause mortality was considered an efficacy and safety endpoint. To assess safety, all adverse events together with an oropharyngeal examination for evidence of candidiasis and inspection of the volar aspect of the forearm for spontaneous bruises were documented. Additionally, at weeks 0, 56, and 104, electrocardiograms were performed.

Of 1,499 patients, 1,323 were randomized and used in the intent-to-treat analysis. No difference was found between estimated overall rates of exacerbations (SFC, 1.28/yr; tiotropium, 1.32/yr; P = 0.656). Similarly, no difference was observed between the study arms for the occurrence of exacerbations requiring hospitalization (16% for SFC arm and 13% for tiotropium arm, P = 0.085). Exacerbations requiring antibiotics occurred less frequently in patients treated with tiotropium (tiotropium, 0.82/yr; SFC 0.97/yr; P = 0.028) whereas those requiring systemic corticosteroids were less frequent in the SFC arm (SFC, 0.69/yr; tiotropium, 0.85/yr; P = 0.039).

Mean SGRQ total score values at screening were 50.3 units for the SFC and 52.3 for the tiotropium treatment groups and improved after the treatment during the run-in period to 48.0 and 48.2 units at baseline, respectively. The total SGRQ score was statistically significantly higher in the tiotropium group than the SFC group at Weeks 32, 56, 80, and 104; however, this statistical difference did not reach the minimum clinically important 4-unit difference between the treatment arms. At Week 104, the percentage of patients who achieved a clinically important improvement in SGRQ score was greater in the SFC than the tiotropium group (32% and 27%, respectively; P = 0.021). No difference in adjusted mean FEV_1 post-dose between the treatments was demonstrated at the completion of the trial.

The INSPIRE investigators reported that mortality was significantly lower in the SFC treatment group; 21 (3%) of SFC patients and 38 (6%) of those in the tiotropium group died (P = 0.032) during the study period. It is important to note that INSPIRE was powered for the efficacy endpoint but was not designed as a mortality trial. There was no independent adjudication of individual fatal cases and patients who did not complete the study were not followed up. No definitive conclusions, therefore, can be drawn from the apparent differences between the two treatment arms.

Overall safety findings, including fatal events, were consistent with a population of patients with severe and very severe COPD. The frequency of adverse events was similar in the two treatment arms with 66% of SFC patients and

62% of those receiving tiotropium reporting some adverse event. COPD exacerbations were reported most frequently. The incidence of serious adverse events was lower with tiotropium. SAEs were reported during treatment by 30% of SFC-treated and 24% of tiotropium-treated patients. Fatal events were reported in 38 (6%) patients in the tiotropium group and in 21 (3%) patients in the SFC group. The rate of pneumonia was higher in the SFC group (8 versus 4% in tiotropium arm) and the hazard ratio for time to reported pneumonia was 1.94 (P = 0.008) for SFC compared with tiotropium over the 2 years. The incidence of reported pneumonias that overlapped with an exacerbation treated with antibiotics was 55% in the SFC group and 48% in the tiotropium group (i.e., the other episodes were not given antibiotic treatment despite the report of pneumonia). A total of 14 patients were withdrawn from the study due to pneumonia (9 in SFC and 5 in tiotropium group). Other adverse events of interest (e.g., fractures, bruising, candidiasis) were infrequent.

Patients randomized to tiotropium were significantly more likely to withdraw from the study than those randomized to SFC as evidenced by the estimated probability of withdrawing before Week 104 of 41.7% in the tiotropium group and 34.5% in the SFC group (hazard ratio of 1.29, P = 0.005). The reported withdrawal rates in the SFC and tiotropium groups are shown in the table below.

	SFC Arm – n (%)	***Tiotropium Arm – n (%)***
Adverse event	67 (10.2)	66 (9.9)
Consent withdrawal	61 (9.3)	82 (12.3)
Loss to follow-up	15 (2.3)	13 (2.0)
Protocol violation	7 (1.1)	8 (1.2)
Failure to meet entry criteria	0	3 (0.5)
COPD exacerbation	37 (5.6)	51 (7.7)
Lack of efficacy	32 (4.9)	38 (5.7)
Other	13 (2.0)	17 (2.6)
Missing	0	1 (0.2)
Total	232 (35.3)	279 (42.0)

SPIRIVA has a well established efficacy and safety profile in patients with COPD.[2] This has been demonstrated by an extensive clinical trial program including over 10,000 patients, and almost eight million patients have benefited from SPIRIVA since it was first introduced in 2002.[3] In addition, the four-year, landmark study **U**nderstanding **P**otential **L**ong-term **I**mpacts on **F**unction with **T**iotropium (UPLIFT) will report data in 2008.

References:

1. Wedzicha JA, Calverley PMA, Seemungal TA, et. al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Resp Crit Care Med* 2008;177:19-26.
2. Kesten S, Jara M, Wentworth C, et al. Pooled clinical trial analysis of tiotropium safety.
3. Data on file. Ingelheim, Germany: Boehringer Ingelheim International GmbH.

SPIRIVA and Possible Elevated Risk of Stroke

On March 18, 2008, the U.S. Food and Drug Administration (FDA) issued an early communication to provide patients and healthcare professionals with emerging drug safety information about a possible increased risk of stroke observed in a pooled analysis of 29 clinical trials among patients taking SPIRIVA.

Boehringer Ingelheim and Pfizer routinely perform safety monitoring of marketed products by evaluating adverse events reported to the company, as well as by conducting epidemiologic studies and clinical trials. Boehringer Ingelheim recently completed a pooled analysis of 29 clinical trials including data from two formulations of SPIRIVA® (HandiHaler® Powder inhalation system and Respimat® soft mist inhalation system) involving more than 13,000 patients (7,856 receiving tiotropium and 5,692 receiving placebo). There was a possible elevated risk of stroke among patients taking tiotropium. Based on data from these studies, the preliminary estimates of the risk of stroke are 8 patients per 1000 patients treated for one year with SPIRIVA®, and 6 patients per 1000 patients treated for one year with placebo (rate ratio (RR) = 1.37, 95% confidence interval (CI) 0.73 – 2.56). This means that the estimated excess risk of any type of stroke due to SPIRIVA is 2 patients for each 1000 patients using SPIRIVA® over a one year period. The results of the analyses were provided to the FDA voluntarily and pro-actively in November 2007. The FDA requested additional data in February 2008, which was submitted in March 2008.

Boehringer Ingelheim and Pfizer concur with the FDA statement: “It is important to interpret these preliminary results with caution. FDA has not confirmed these analyses. Pooled analyses can provide early information about potential safety issues. However, these analyses have inherent limitations and uncertainty that require further investigation using other data sources.” In dialogue with the authority, Boehringer Ingelheim and Pfizer are continuing to evaluate information from a variety of sources.

Upon review of available literature, there are presently no links relating anticholinergic medications in general or tiotropium specifically to the risk of stroke. The effect estimate from the pooled analysis is imprecise and inconclusive.

Ongoing clinical trials (including UPLIFT) that will be completed in 2008 will approximately double the amount of patient exposure to tiotropium presently available from all clinical trials combined. These data will be available in the near future, at which time we will have substantially more prospective evidence than is currently available.

The efficacy and safety profile of SPIRIVA® have been demonstrated by an extensive clinical trial development program, which includes over 13,000 patients. Boehringer Ingelheim and Pfizer continue to support the present efficacy and safety profile of SPIRIVA® when used in accordance with its approved labeling. Boehringer Ingelheim and Pfizer are committed to patient safety and to working closely with the FDA to increase our understanding of what this information means for patients and physicians. We will keep the FDA apprised of the results from on-going studies as they become available.

UPLIFT Trial

The purpose of the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial is to determine whether treatment with SPIRIVA reduces the rate of decline of FEV_1 over time in patients with COPD. It is a four year randomized, double-blind, placebo-controlled, parallel group clinical trial involving thirty-seven countries (approximately 500 investigational sites) which has enrolled approximately 6000 patients, 3000 receiving SPIRIVA.

The co-primary endpoints are: (1) the yearly rate of decline in trough FEV_1 from day 30 (steady state) until completion of double-blind treatment. Trough FEV_1 is the pre-dose value measured approximately 24 hours after the previous dose of study drug. (2) the yearly rate of decline in FEV_1 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from day 30 (steady state) until completion of double-blind treatment.

Secondary endpoints are: (1) Mean yearly rate of decline in FEV_1, FVC and SVC 90 minutes post ipratropium, including 30 minutes post albuterol inhalation, from day 1 until completion of the trial (30 days post study treatment). (2) Mean yearly rate of decline in FVC and SVC 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from day 30 until completion of double-blind treatment. (3) Mean yearly rate of decline in FEV_1, FVC and SVC prior to ipratropium and albuterol inhalation from day 1 until completion of the trial (30 days post study drug treatment). (4) Mean yearly rate of decline in trough FVC and SVC from day 30 until completion of double-blind treatment. Trough FVC and SVC are the pre-dose values measured approximately 24 hours after the previous dose of study drug. (5) Frequency of COPD exacerbations. (6) Time to first exacerbation. (7) Number of patients with COPD exacerbations. (8) Number of exacerbation days. (9) Number of days between exacerbations. (10) Number of patients with COPD exacerbations leading to hospitalizations. (11) Time to exacerbation leading to hospitalization. (12) Number of hospitalizations for exacerbations. (13) Number of days hospitalized for COPD exacerbations. (14) Mean yearly decline in SGRQ total score. (15) Mortality (respiratory and all-cause).

The results of the UPLIFT trial are expected to be reported later this year (2008).